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(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING LIPASE INHIBITORS

(57) Abstract

Orally administrable pharmaceutical composition containing an inhibitor of gastrointestinal lipase, one (or more) additive(s) of the group consisting of poorly digestible, poorly fermentable, hydrophilic and/or hydrocolloidal food grade thickeners and emulsifiers, and auxiliary excipients.

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PHARMACEUTICAL COMPOSITIONS CONTAINING LIPASE INHIBITORS

The present invention relates to pharmaceutical compositions containing an inhibitor of gastrointestinal lipases, one (or more) additive(s) of the group consisting of poorly digestible, poorly fermentable, hydrophilic and/or hydrocolloidal food grade thickeners and emulsifiers, and excipients.

An example of an inhibitor of gastrointestinal lipases is orlistat, previously known as tetrahydrolipstatin or THL. Orlistat reduces the absorption of dietary fat. Its use for the control or prevention of obesity and hyperlipidaemia is described in US patent 4 598 089.

Anal leakage of oil (oily spotting) is an adverse effect which is occasionally observed in patients treated with lipase inhibitors. This phenomenon reflects physical separation of some liquid unabsorbed dietary fat from the bulk of unabsorbable solids in the lower large intestine. This physical separation and thus anal leakage of oil can be prevented with the pharmaceutical compositions of the present invention.

In the US patent 5 447 953 it has been demonstrated that by combining a lipase inhibitor with substantial amounts of water-insoluble crude fibers, the inhibiting effect on fat absorption can be increased. This synergistic effect is likely attributable to acceleration of gastrointestinal transit of food by the water-insoluble fiber component. The consequent shortening of the time period available for fat digestion combined with the reducing effect on lipase activity intensifies the inhibitory effect on fat absorption.

Surprisingly, it has now been found that the separation of unabsorbed oil from the feces and thus anal oil leakage can be reduced or prevented, when a lipase inhibitor such as orlistat is administered in combination with low amounts of one or more poorly digestible, poorly

fermentable, hydrophilic and/or hydrocolloidal food grade thickeners and/or emulsifiers.

5 The invention is also concerned with the use of poorly digestible, poorly fermentable hydrophilic and/or hydrocolloidal food grade thickeners and/or emulsifiers for the combined simultaneous, separate or chronologically spaced use with lipase inhibitors, e.g. orlistat, in the treatment of obesity and hyperlipaemia.

10 The invention is further concerned with the use of the above thickeners and/or emulsifiers for treating or preventing the syndrome of anal leakage of oil occurring after the administration of a lipase inhibitor, such as orlistat, or after ingestion of food containing poorly absorbable or non-absorbable fats or oils or undigestible oily fat substitutes.

15 Further examples of lipase inhibitors which can be used in the scope of the present invention are lipstatin, panclicins, hesperidin, ebelactones, esterastin and their derivatives, and valilactone.

20 As thickeners there can be cited water soluble natural, synthetic or semisynthetic polysaccharides, such as methylcellulose, xanthan gum, psyllium seed, ispaghula husk, plantago ovata seeds, karaya gum and mixtures of such compounds:

Methyl cellulose is the methyl ether of cellulose. It is slowly soluble in water, giving a viscous, colloid solution.

25 Xanthan gum is a biosynthetic hydrocolloidal high molecular weight exopolysaccharide produced by pure culture fermentation of *Xanthomonas campestris*. It contains D-glucose, D-mannose, and D-glucuronic acid as the dominant hexose units and is manufactured as the sodium, potassium, or calcium salt.

30 Psyllium seed husk, seed coat is a source of soluble fibre. It comprises cellulose containing walls of endosperm, and mucilage containing epidermis of small dried ripe seeds. A colorless transparent mucilage forms upon contact with water.

Ispaghula husk is psyllium hydrophilic mucilloid. It comprises the epidermis and collapsed adjacent layer of *Plantago* species, e.g. *Pl. psyllium*. It swells rapidly upon contact with water to form a stiff mucilage.

5 *Plantago ovata* seeds (seed husk and seed coat) is a source of soluble fibre. It comprises cellulose containing walls of endosperm, and mucilage containing epidermis of small dried ripe seeds. A colorless transparent mucilage forms upon contact with water.

10 Karaya gum is a hydrocolloidal exudate or gum from *Sterculia* species. It forms a homogenous adhesive gelatinous mass upon contact with water.

Examples of these types of thickeners are contained in OTC products and/or food additives, such as:

15 METHOCEL A4M, a trademark of Dow Chemical Co. for a high viscosity methyl cellulose,

KELTROL TF, a trademark of Merck & Co. Inc., Rahway NJ, for xanthan gum,

MUCILAR; psyllium seed (*Psyllii seminis testa*), a product of Spirig AG, CH-4622 Egerkingen,

20 METAMUCIL, ispaghula husk (*Ispaghulae testae pulvis*) a product of Procter & Gamble, CH-1211 Geneve 2,

AGIOCUR, *plantago ovata* seeds, a product of Madaus AG, D-5000 Köln 91,

25 NORMACOL MITE, a trademark of Norgine Ltd., Great Britain, for karaya gum,

POLY-KARAYA, a trademark of Delalande for karaya gum of Interdelta SA, CH-1701 Fribourg.

30 A further example of a thickener is FIBERCON (polycarbophil), a trademark of Lederle Laboratories Division, American Cyanamid Co., Pearl River NY, for the calcium salt of a synthetic loosely crosslinked hydrophilic resin of the polycarboxylate type.

As emulsifiers which can be utilized in the compositions of the invention, there can be cited saccharose polyesters, such as Ryoto Sugar

Esters, e.g. Ryoto Sugar Ester S-170. Ryoto Sugar Esters are a trade name of Mitsubishi-Kasi Foods Corp., Chuo-Ku, Tokyo 104, for sucrose fatty acid esters. Ryoto Sugar Ester S-170 contains sucrose stearic acid polyesters.

5 Examples of excipients which can be used in the pharmaceutical compositions of the invention are binders, diluents and lubricants, such as AVICEL, polyvinyl pyrrolidone (povidone), talc, stearic acid and sodium stearyl fumarate; sweeteners, such as sorbitol, glucose, 10 saccharose, saccharine-sodium salt and sodium cyclamate; flavour agents, such as passion fruit, citron and limette; flavour enhancers, such as citric acid, monosodium citrate, sodium chloride and chinine sulfate; effervescing agents, such as sodium bicarbonate and tartaric acid; disintegrants, such as sodium starch glycolate; antimicrobial 15 agents, such as p-hydroxybenzoic acid methyl or propyl ester; detergents, such as sodium lauryl sulfate, and colouring agents, such as β -carotene.

AVICEL essentially comprises microcrystalline cellulose. It is available from FMC Corporation, Pharmaceutical Division, 1735 Market Street, Philadelphia, PA 19103, e.g. as AVICEL RC-591 or 20 CL-611, which are mixtures of microcrystalline cellulose (about 92%) and carboxymethylcellulose sodium (about 8%), AVICEL PH 101 or PH 105, which is microcrystalline cellulose with an average particle size of 50 or 20 μ , respectively; AVICEL CE-15 a mixture of microcrystalline cellulose and guar gum.

25 As indicated above, anal leakage of oil, occasionally observed with the therapeutic use of lipase inhibitors such as orlistat, can be reduced or prevented with the pharmaceutical compositions of the invention. This is illustrated by the following in vivo experiments:

30 Rats maintained on high fat diet were used as model. Inhibition of fat absorption by diet-admixed orlistat provoked anal leakage of liquid oil. However, the amount of oil leakage could not easily be determined. Due to coprophagia and extensive grooming activity the rats distributed the oil to a large extent over their fur. Moreover, this stressful condition of unsuccessful grooming provoked considerable excitation of the

animals. The area of greasy fur increased in proportion to the amount of unabsorbed fat and was reduced by dietary admixture of selected examples of the above defined food additives. However, for reasons of animal care for comparative evaluation of the additives a surrogate parameter was used to assess effects on oil leakage. Following a meal containing orlistat, unabsorbed fat is temporarily stored in the caecum of the rat prior to excretion. The fat is partly present as floating liquid oil, partly associated with unabsorbable solids. In validation studies it could be demonstrated that the effect of food additives to bind and sequester unabsorbed liquid oil in the solid phase of the caecum is a reliable surrogate parameter predictive for a corresponding reduction of subsequent oil leakage.

The high fat basal diet used contained by weight 56% lab chow, 12% glucose and 32% olive oil. Food additives were supplemented at three levels, accounting for 12.4, 4.5 and 1.2% of the composite diet by weight. Control diets were supplemented with a corresponding amount of starch. All diets were moistened with water to a similar consistency to facilitate acceptability by the animals. Groups of 6-7 female rats (body weight: 120-140 g) were allocated to each diet. After dietary adaptation for one week, the rats were fasted for 24 hours and on the subsequent experimental day the diets were supplied as single meal (basal diet: 4.25 g, additives or starch: 0.6, 0.2 and 0.05 g). In order to completely block absorption of oil and thus produce a defined amount of unabsorbed fat a high dose of orlistat (45 mg) was dissolved in the olive oil fraction (1.5 ml) of the meal. The animals were sacrificed three hours after supplying the meal. At this point in time the caecum contained the largest fraction of administered dietary oil. To determine the relative amounts of bound and free oil in the caecum, the caecal contents were centrifuged (2000 g, 30 min) and the lipid content of the oil/water and solid phase was quantitated gravimetrically following extraction with solvent.

The food additives tested in the first experimental series were methylcellulose (MC), Ryoto sugar ester S-170 (RS) and xanthan gum (XG). The fat content of the liquid and solid phases in the caecum was expressed as percentage of the amount of oil supplied with the meal. Mean values for experimental groups fed the additives, as compared to

controls (where the thickening or emulsifying additive was replaced by the corresponding weight of starch(ST)), are shown in the following table. For statistical assessment of the effect of the additives, Student's t-test was used: n.s. = $p > 0.05$, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

5

Fat content in caecum in % of the amount of oil supplied:

additive	oil phase	solid phase
MC 0.05 g	24.8 ^{n.s.}	16.8 *
ST 0.05 g	25.4	13.4
MC 0.20 g	17.0 **	29.2 ***
ST 0.20 g	24.6	13.2
MC 0.60 g	5.0 ***	32.9 ***
ST 0.60 g	37.9	9.6
RS 0.05 g	18.3 ^{n.s.}	13.6 *
ST 0.05 g	23.6	9.0
RS 0.20 g	22.4 ^{n.s.}	23.3 ***
ST 0.20 g	24.2	11.0
RS 0.60 g	3.1 ***	37.1 ***
ST 0.60 g	15.8	11.9
XG 0.05 g	12.7 ***	20.3 ***
ST 0.05 g	23.6	9.0
XG 0.20 g	1.1 ***	23.2 ***
ST 0.20 g	24.2	11.0
XG 0.60 g	0.7 ***	18.9 ***
ST 0.60 g	23.6	10.9

As mentioned above 0.6, 0.2 and 0.05 g of food additive provided with the test meal correspond to 12.4, 4.5 and 1.2% by weight in the water-free composite diet.

5 The results shown above clearly demonstrate that in animals administered orlistat in combination with an additive according to the invention, the fraction of unabsorbed fat sequestered in the solid phase of the caecum was significantly increased (and liquid oil reduced) in comparison to control animals supplied with a corresponding amount of starch. Accordingly, the additives are effective in reducing or
10 preventing anal leakage of liquid oil.

Using the same experimental procedure several OTC products containing additives according to the invention as well as water-insoluble crude fiber products were evaluated in a second experimental series. To ensure a relevant comparison of the products their variable
15 content of active additive or fiber was taken into account. Accordingly, the amount of each product added to the diet was chosen in such a way that all the test meals contained the same amount of active additive or fiber (0.2 g, 4.5% by weight). The results of these experiments are given in the following table:

20 Fat content in caecum in % of the amount of oil supplied:

OTC product	solid phase
AGIOCUR 0.30 g	20 ***
FIBERCON 0.35 g	18 ***
Starch Control 0.20 g	12
NORMACOL MITE 0.32 g	19 **
METAMUCIL 0.41 g	17 **
Starch Control 0.20 g	13
POLY-KARAYA 0.50 g	20 ***
Wheat bran 0.42 g	15 n.s.
Oat bran 1.60 g	11 n.s.
Starch Control 0.20 g	12

As mentioned above, the weight of OTC products indicated in the table correspond to 0.2 g active thickening or emulsifying additive or water-insoluble fiber.

5 The data demonstrate binding and sequestering of caecal oil and thus efficacy in preventing anal leakage of oil for the OTC compounds AGIOCUR, FIBERCON, METAMUCIL, NORMACOL MITE and POLY-KARAYA. Moreover, the results show as well the superiority of
10 additives according to the invention, as exemplified by POLY-KARAYA, over crude water-insoluble fibers, such as oat and wheat bran (no significant effect), which have been proposed in US patent 5 447 953 to improve the inhibitory effect on fat absorption.

15 The compositions of the invention conveniently contain 1 to 300, preferably from 3 to 30 parts by weight of an emulsifier or thickener for 1 part by weight of orlistat or another lipase inhibitor. They conveniently further contain from 1 to 500, preferably from 3 to 200 parts by weight of auxiliary excipients for 1 part by weight of the lipase inhibitor.

20 The compositions of the invention can be in the form of tablets, capsules or liquid formulations, that may be reconstituted from powder,

granules, pellets, standard or effervescent tablets. They can also be formulated as chewable tablets or lozenges. Furthermore, the compositions can also be incorporated into food preparations, such as wafers, crackers or bisquits.

5 The composition of the invention can also be in the form of a commercial pack containing a lipase inhibitor, such as orlistat, and one or more of the above mentioned thickeners and emulsifiers, with instructions for its use for the simultaneous, separate or chronologically spaced use in the treatment of obesity or hyperlipidaemia.

10 For the treatment or prevention of obesity or hyperlipidaemia, a composition of the invention containing from 50 to 500 mg of orlistat or another lipase inhibitor and from 150 mg to 15 g of an emulsifier or thickener can be administered orally once, twice or three times per day.

15 A preferred composition of the invention is a chewable tablet for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of karaya gum as the thickener, wherein the dosage is from 50 to 150 mg of orlistat and from 3 to 30 parts by weight of karaya gum or xanthan gum per 1 part by weight of orlistat, most preferably wherein the dosage is about 60 mg of orlistat and about 1.5 g of karaya
20 gum or xanthan gum.

 A method of preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of orlistat, comprises orally administering from 1 to 3 chewable tablets per fat containing main meal, the dosage of each tablet being from 50 to 150
25 mg of orlistat and from 3 to 30 parts by weight of karaya gum or xanthan gum per 1 part by weight of orlistat. Preferably, this method comprises orally administering orlistat and karaya gum or xanthan gum in a dosage amount of about 100 mg of orlistat and of about 2 g of karaya gum or xanthan gum per fat containing main meal.

30 The following non-limiting examples illustrate pharmaceutical preparations that can be produced in a manner known per se:

Example 1

Powder for reconstitution:

	Orlistat	0.12 g
	Xanthan gum	1.20 g
5	Sorbitol	9.91 g
	AVICEL CL 611	1.20 g
	β -Carotene 1% CWS	0.06 g
	Citric acid	0.10 g
	p-Hydroxybenzoic acid methyl ester	0.15 g
10	p-Hydroxybenzoic acid propyl ester	0.03 g
	Flavouring agent (passion fruit)	0.13 g
	AVICEL PH 105	4.00 g
	Monosodium citrate	1.00 g
	Saccharine-sodium salt	<u>0.10 g</u>
15	Total	18.00 g

An oral suspension can be obtained by adding tap-water to the above powder to a volume of about 50 ml.

Example 2

20 Chewable tablets:

	Orlistat	0.060 g
	Karaya gum	1.500 g
	Polyvinyl pyrrolidone	0.750 g
	Sorbitol	0.970 g
25	AVICEL CE-15	1.000 g
	Talc	0.480 g
	Stearic acid (micro-fine powder)	0.240 g
	Total	5.000 g

30 The indicated amounts of orlistat, karaya gum, polyvinyl pyrrolidone, sorbitol and AVICEL CE 15 are mixed and sieved. The talc and stearic acid are sieved and mixed with the above obtained

mixture. The material is then compressed to chewable tablets with a diameter of 2 cm and a weight of 5 g.

Example 3

5 Pelletized formulation containing an emulsifier:

1. Orlistat pellets:

	Finely milled orlistat	120 mg
	Microcrystalline cellulose	93.6 mg
	Sodium starch glycolate	7.2 mg
	Sodium lauryl sulfate	7.2 mg
10	Povidone	12 mg
	Total	240 mg

For a batch size of 4 kg pellets the following procedure is applied:

15 Sodium lauryl sulfate (120 g) and povidone (200 g) are dissolved in q.s. water. The solution is cooled to 10-15°C → A. Orlistat (2000 g), microcrystalline cellulose (1560 g) and sodium starch glycolate (120 g) are pre-mixed → B.

20 Solution A is given to pre-mix B and kneaded. The resulting material is extruded to spaghettis. This extrudate is spheromized at 700 rpm. The obtained cylinder-shaped wet pellets are dried in a fluidized bed dryer and then sieved. The 0.5-1.25 mm size fractions are collected as orlistat pellets in closed containers.

2. Emulsifier part.

	Ryoto sugar ester S-170	600 mg
	Microcrystalline cellulose	312 mg
25	Sodium starch glycolate	15 mg
	Povidone	15 mg
	Talc	18 mg
	Total	960 mg

30 For a batch size of 16 kg pellets the following procedure is applied:

Sugar ester (10 kg) is liquefied by heating to 60°C.
Microcrystalline cellulose (5.2 kg), sodium starch glycolate (0.4 kg) and povidone (0.4 kg) are added. The mass is kneaded under cooling to room temperature, then extruded through an extrusion plate with nominal
5 mesh size of 0.7 mm. The fatty extrudate is cut into pieces of 1 mm length and the resulting mass is dusted with talc in a mixer.

Orlistat pellets (2.4 kg) and emulsifier pellets (9.6 kg) are mixed. The mixture is filled into sachets at a fill weight of 1.2 g, corresponding to 120 mg of orlistat and 600 mg of sugar ester.

Claims

5 1. Orally administrable pharmaceutical composition containing an inhibitor of gastrointestinal lipase, one (or more) additive(s) of the group consisting of poorly digestible, poorly fermentable, hydrophilic and/or hydrocolloidal food grade thickeners and emulsifiers, and auxiliary excipients.

2. A composition as in claim 1, wherein the additive is a poorly digestible, poorly fermentable, hydrophilic and hydrocolloidal food grade thickener.

10 3. A composition as in claim 2, wherein the food grade thickener comprises methylcellulose, xanthan gum, psyllium seed, ispaghula husk, plantago ovata seeds, karaya gum or mixtures thereof.

4. A composition as in claim 1, wherein the additive is an emulsifier.

15 5. A composition as in claim 4, wherein the emulsifier is a saccharose polyester.

6. A composition as in claim 2 or 3 comprising 1 to 300 parts by weight of a thickener per 1 part by weight of an inhibitor of gastrointestinal lipase.

20 7. A composition as in claim 4 comprising 1 to 300 parts by weight of an emulsifier per 1 part by weight of an inhibitor of gastrointestinal lipase.

8. A composition as in any one of claims 1-7, wherein the inhibitor of gastrointestinal lipase is orlistat.

25 9. The use of one (or more) compound(s) of the group consisting of poorly digestible, poorly fermentable, hydrophilic and/or hydrocolloidal food grade thickeners and emulsifiers for treating or preventing the syndrome of anal leakage of oil occasionally occurring after the administration of an inhibitor of gastrointestinal lipase, such as

orlistat, or after ingestion of food containing poorly absorbable or non-absorbable fats or oils or undigestible oily fat substitutes.

5 10. A composition as in claim 3 or 8, which is a chewable tablet for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of karaya gum or xanthan gum as the thickener, wherein the dosage is from 50 to 150 mg of orlistat and from 3 to 30 parts by weight of karaya gum or xanthan gum per 1 part by weight of orlistat.

10 11. The chewable tablet as in claim 10, wherein the dosage is about 60 mg of orlistat and about 1.5 g of karaya gum or xanthan gum.

15 12. A method of preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of orlistat, comprising orally administering from 1 to 3 chewable tablets per fat containing main meal, the dosage of each tablet being from 50 to 150 mg of orlistat and from 3 to 30 parts by weight of karaya gum or xanthan gum per 1 part by weight of orlistat.

20 13. A method of preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of orlistat, comprising orally administering orlistat and karaya gum in a dosage amount of about 100 mg of orlistat and of about 2 g of karaya gum or xanthan gum per fat containing main meal.

INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/EP 99/05607

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/365 A61K9/00 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 447 953 A (ISLER DOROTHEA ET AL) 5 September 1995 (1995-09-05) cited in the application column 1, line 31 - line 51 column 2, line 19 - line 38 column 2, line 65 - column 3, line 11 column 3, line 26 - line 58 claims; examples 1,2	1,2,8
X	WO 98 34607 A (HOFFMANN LA ROCHE) 13 August 1998 (1998-08-13) page 2, line 7 - line 28 page 5, line 14 - line 24 claims; examples	1,2,4,6, 8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05607

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	--- CHEMICAL ABSTRACTS, vol. 127, no. 20, 17 November 1997 (1997-11-17) Columbus, Ohio, US; abstract no. 277507, MIZUGUCHI, YOJI: "Nutrient supplement foods containing taheebo extract and natural minerals" XP002123841 abstract & JP 09 252746 A (NIPPON KANKYO YAKUHI K. K., JAPAN) 30 September 1997 (1997-09-30)	1,2,4-7
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X	--- WO 92 17077 A (CURTICE BURNS INC) 15 October 1992 (1992-10-15) page 3, line 1 - line 22 page 4, line 33 -page 7, line 13 claims 1-3,6,14; examples 1,3	9
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 05607

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9, 12 and 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest:

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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International Application No

PCT/EP 99/05607

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